

REMARKS

The amendments above serve to define the invention using variables "M" and "L¹" consistent with other copending applications. Other amendments have been made to differentiate each side of the urea functional group. Only the amendment to the element "L¹" discussed below, has been made to distinguish the reference WO 97/17328.

Rejection Under 35 USC §103

The substituent L¹, an element within all of the compounds claimed, has been limited by the above amendments and does not encompass 6,7- dialkoxy -4-quinoline or 6,7-dialkoxy-4-quinazoline in that where L¹ is benzopyridine, it can optionally have only have one alkoxy substituent. The structures for Group B of formula I encompass quinoline and quinazoline, however, these structures are directly bound to a urea group, which is not shown in the general formula of WO 97/17329. In compound claims 1-14, the group corresponding to Group A of formula I can be phenyl or naphthyl. The compounds now defined by claims 1-14 are structurally distinct from the compounds generically disclosed by WO 97/17329 and so they are not obvious in view of WO 97/17329.

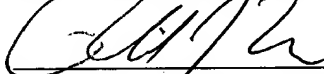
The method claims have not been amended to limit L¹ of the compounds used with respect to alkoxy substitution on quinoline and quinazoline in that the abstract of WO 97/17329 does not suggest the compounds of this invention are effective raf kinase inhibitors.

In that the neither compounds nor the methods of this invention are suggested by this reference, withdrawal of the rejection under 35 USC §103 based on this reference is appropriate.

Based on the above remarks, Applicants respectfully request withdrawal of the rejection based on WO 97/017329 and expansion of the examined subject matter to the full scope of the claims. Consideration of the Information Disclosure Statement submitted on December 30, 2002, is also requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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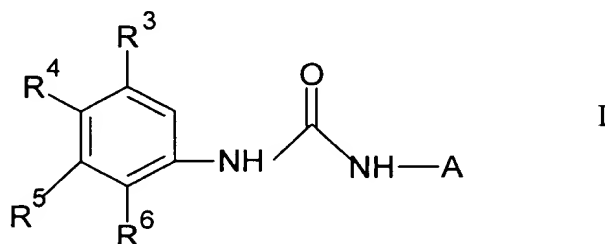
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Date: March 13, 2003

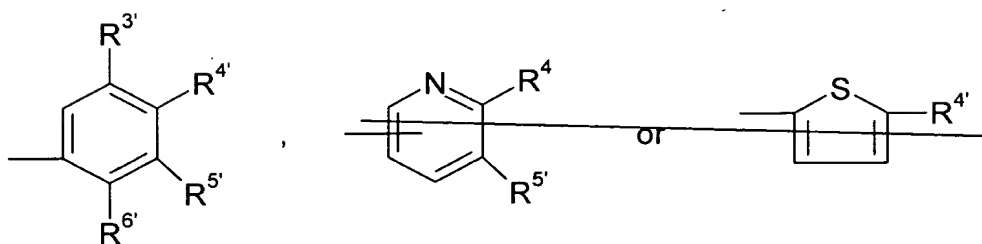
VERSION WITH MARKINGS TO SHOW THE CHANGES MADE

1. (Amended) A compound of formula I:



wherein

A is



R^3 , R^4 , R^5 and R^6 are each, independently, H, halogen, NO_2 , C_{1-10} -alkyl, optionally substituted by halogen up to perhaloalkyl, C_{1-10} -alkoxy, optionally substituted by halogen up to perhaloalkoxy, C_{1-10} -alkanoyl, optionally substituted by halogen up to perhaloalkanoyl,

C_{6-12} aryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy, or C_{5-12} hetaryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy,

and either one of R^3 - R^6 can be X-Y R^3 , R^4 , R^5 and R^6 is -M-L¹;

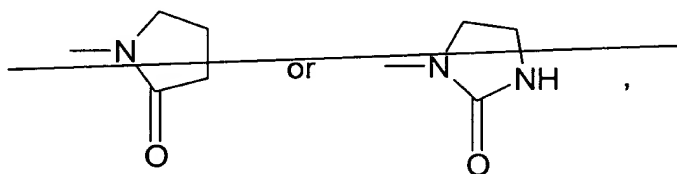
or two adjacent R^3 - R^6 can together be of R^3 , R^4 , R^5 and R^6 together are an aryl or hetaryl ring with 5-12 atoms, optionally substituted by C_{1-10} -alkyl, , halo-substituted C_{1-10} -alkyl up to

perhaloalkyl, C₁₋₁₀-alkoxy, halo-substituted C₁₋₁₀-alkoxy, up to perhaloalkoxy, C₃₋₁₀-cycloalkyl, C₂₋₁₀-alkenyl,

C₁₋₁₀-alkanoyl, C₆₋₁₂-aryl, C₅₋₁₂-hetaryl; C₆₋₁₂-aralkyl, C₆₋₁₂-alkaryl, halogen; NR¹R¹;

-NO₂; -CF₃; -COOR¹; -NHCOR¹; -CN; -CONR¹R¹; -SO₂R²; -SOR²; -SR²; in which R¹ is H or C₁₋₁₀-alkyl, optionally substituted by halogen up to perhaloalkyl and R² is C₁₋₁₀-alkyl, optionally substituted by halogen, up to perhaloalkyl, ~~perhalo with S(O₂) optionally incorporated in the aryl or hetaryl ring;~~

R^{3'}, R^{4'}, R^{5'} and R^{6'} are independently H, halogen, C₁ - C₁₀ alkyl, optionally substituted by halogen up to perhaloalkyl,



C₁ - C₁₀ alkoxy optionally substituted by halogen up to perhaloalkoxy ~~or X-Y, and either one of R^{4'}, R^{5'} or R^{6'} is X-Y~~ or two adjacent of R^{3'}, R^{4'}, R^{5'} and R^{6'},

together with the base phenyl, form a naphthyl group, are a hetaryl ring with 5-12 atoms optionally substituted by halogen up to perhalo, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkanoyl, C₆₋₁₂ aryl, C₅₋₁₂ hetaryl or C₆₋₁₂ aralkyl;

R^{6'} — is additionally ~~NHCOR¹, NR¹COR¹ or NO₂;~~

R¹ — is C₁₋₁₀-alkyl ~~optionally substituted by halogen up to perhalo;~~

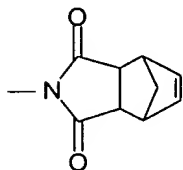
R^{3'} — is H, halogen, C₁ - C₁₀-alkyl ~~optionally substituted by halogen up to perhaloalkyl, C₁ - C₁₀ alkoxy, optionally substituted by halogen up to perhaloalkoxy;~~

X M is -CH₂-, -S-, -N(CH₃)-, -NHC(O)- -CH₂-S-, -S-CH₂-, -C(O)-, or -O-; and

X — is additionally a single bond where Y is pyridyl; and

B

Y L^1 is phenyl, optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen, OH, -SCH₃, NO₂ or,



pyridyl, optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen, OH, -SCH₃, or NO₂,
naphthyl, optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen, OH, -SCH₃ or NO₂,

pyridone, optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen, OH, -SCH₃ or NO₂,

pyrazine, optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen, OH, -SCH₃ or NO₂,

pyrimidine, optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen, OH,

-SCH₃ or NO₂,

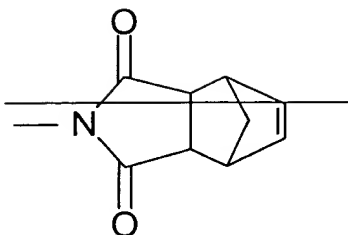
benzodioxane benzodioxane, optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen,
OH,

-SCH₃ or NO₂,

benzopyridine, optionally substituted by C₁₋₁₀-alkyl, one C₁₋₁₀-alkoxy, halogen, OH,

-SCH₃ or NO₂ or

benzothiazole, [each] optionally substituted by, C₁₋₁₀ alkyl C₁₋₁₀ alkoxy, halogen, OH, -SCH₃ or
; NO₂; [~~or, where Y is phenyl by~~



or a pharmaceutically acceptable salt thereof;

~~with the proviso that if X is O or S, R^{3'} and R^{6'} are H, and Y is phenyl unsubstituted by OH, then R⁶ is alkoxy.~~

2. (Amended) A compound according to claim 1, having a pKa greater than 10.

3. (Amended) A compound according to claim 1, wherein

R³ is H, halogen or C₁₋₁₀-alkyl, optionally substituted by halogen, up to perhaloalkyl;

R⁴ is H, halogen or NO₂;

R⁵ is H, halogen or C₁₋₁₀-alkyl;

R⁶ is H, C₁₋₁₀-alkoxy, thiophene, pyrrole or methyl substituted pyrrole,

R^{3'} is H, halogen, C₄₋₁₀-alkyl, ~~CH₃~~, or CF₃ and

R^{6'} is H, halogen CH₃, CF₃ or -OCH₃.

4. (Amended) A compound according to claim 1, wherein

$R^3 R^{3'}$ is C_{4-10} -alkyl, Cl, F or CF_3 ;

$R^4 R^{4'}$ is H, Cl or F ~~or~~ NO_2 ;

$R^5 R^{5'}$ is H, Cl, F or C_{4-10} -alkyl; and

$R^6 R^{6'}$ is H or OCH_3 .

5. (Amended) A compound according to claim 4, wherein $R^3 R^{3'}$ or $R^5 R^{5'}$ is t-butyl.

6. (Amended) A compound according to claim 1, wherein $X M$ is $-CH_2-$, $-N(CH_3)-$ or $-NHC(O)-$.

7. (Amended) A compound according to claim 6, wherein $Y L^1$ is phenyl or pyridyl.

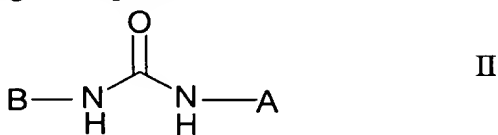
8. (Amended) A compound according to claim 1, wherein $X M$ is $-O-$.

9. (Amended) A compound according to claim 8, wherein $Y L^1$ is phenyl, pyridyl pyridone or benzothiazole.

10. (Amended) A compound according to claim 1, wherein $X M$ is $-S-$.

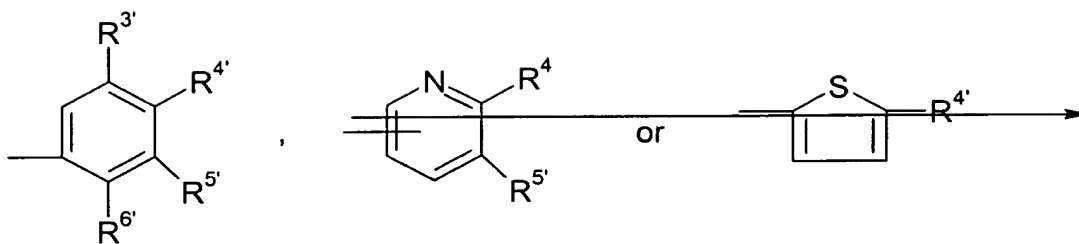
11. (Amended) A compound according to claim 10, wherein $Y L^1$ is phenyl or pyridyl.

15. (Amended) A method for the treatment of a cancerous cell growth mediated by raf kinase, comprising administering a compound of formula II:



or a pharmaceutically acceptable salt thereof wherein

A is



B is a substituted or unsubstituted, up to tricyclic bicyclic aryl or heteroaryl moiety of up to 30 12 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is substituted it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n , wherein n is 0-3 and each W is independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{C}(\text{O})-\text{R}^7$, $-\text{NO}_2$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_1\text{-C}_{10}$ alkenoyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{14}$ aryl, optionally substituted with halogen, $\text{C}_1\text{-C}_{10}$ alkyl, or $\text{C}_1\text{-C}_{10}$ alkoxy; $\text{C}_7\text{-C}_{24}$ alkaryl, optionally substituted with halogen, $\text{C}_1\text{-C}_{10}$ alkyl, or $\text{C}_1\text{-C}_{10}$ alkoxy; $\text{C}_3\text{-C}_{13}$ heteroaryl, optionally substituted with halogen, $\text{C}_1\text{-C}_{10}$ alkyl, or $\text{C}_1\text{-C}_{10}$ alkoxy; $\text{C}_4\text{-C}_{23}$ alkheteroaryl, optionally substituted with halogen, $\text{C}_1\text{-C}_{10}$ alkyl, or $\text{C}_1\text{-C}_{10}$ alkoxy; substituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted $\text{C}_2\text{-C}_{10}$ alkenyl, substituted $\text{C}_1\text{-C}_{10}$ alkenoyl, substituted $\text{C}_1\text{-C}_{10}$ alkoxy, substituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted $\text{C}_4\text{-C}_{23}$ alkheteroaryl and $-\text{M-L}^1\text{-Ar}$;

wherein if W is a substituted group which does not contain aryl or hetaryl moieties, it is substituted by one or more substituents independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, NO_2 , $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$ and halogen up to per-halo;

wherein each R^7 is independently selected from H, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_3\text{-C}_{10}$

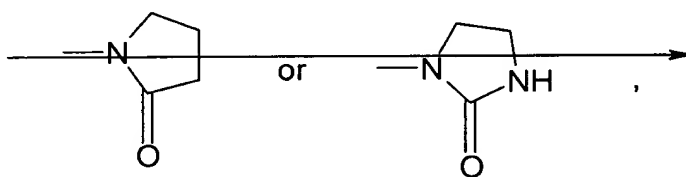
cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ hetaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halo substituted C₂-C₁₀ alkenyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ hetaryl,

wherein $\Theta \underline{M}$ is - O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -NR⁷C(O) NR⁷R⁷-, -NR⁷C(O)-, -C(O)NR⁷-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-, -CHX^a, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-,

m = 1-3, and X^a is halogen; and

$\text{Ar } \underline{L}^1$ is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur, which is unsubstituted or substituted by halogen up to per-halo and optionally substituted by Z_{n1}, wherein n₁ is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -C(O)- NR⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -C(O)R⁷, -NR⁷C(O)R⁷, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ hetaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, substituted C₁-C₁₀ alkyl, substituted C₃-C₁₀ cycloalkyl, substituted C₇-C₂₄ alkaryl and substituted C₄-C₂₃ alkheteroaryl; wherein the one or more substituents of Z is selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷ and -NR⁷C(O)OR⁷,

wherein R^{3'}, R^{4'}, R^{5'} and R^{6'} are each independently H, halogen, C₁₋₁₀-alkyl, optionally substituted by halogen up to perhaloalkyl,



C₁-C₁₀ alkoxy, optionally substituted by halogen up to perhaloalkoxy or -X-Y, and

~~either one of R^{4'}, R^{5'} or R^{6'} is -X-Y or two adjacent of R^{3'}, R^{4'}, R^{5'} and R^{6'} together with the base phenyl, form a naphthyl group, are a hetaryl ring with 5-12 atoms optionally~~

substituted by halogen up to perhalo, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkanoyl, C₆₋₁₂ aryl, C₅₋₁₂ hetaryl or C₆₋₁₂ aralkyl;

~~R⁶⁺ is additionally NHCOR^+ , NR^+COR^+ or NO_2 ;~~

~~R⁺ is C₁₋₁₀ alkyl optionally substituted by halogen up to perhalo;~~

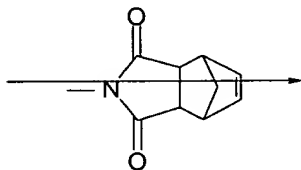
~~R²⁺ is independently H, halogen, C₁₋₁₀ alkyl, optionally substituted by halogen up to perhaloalkyl, C₁₋₁₀ alkoxy, optionally substituted by halogen up to perhaloalkoxy;~~

~~X is CH_2 , S , $\text{N}(\text{CH}_3)$, $\text{NHC}(\text{O})$, CH_2S , $\text{C}(\text{O})$, or O ;~~

~~X is additionally a single bond where Y is pyridyl; and~~

~~Y is phenyl, pyridyl, naphthyl, pyridone, pyrazine, pyrimidine, benzodioxane, benzopyridine or benzothiazole, each optionally substituted by~~

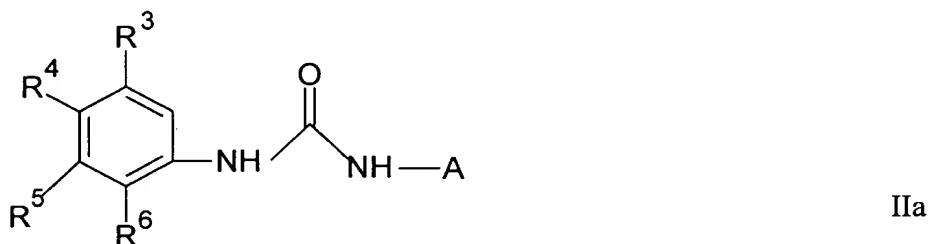
~~— C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halogen, OH, SCH_3 , or NO_2 or, where Y is phenyl, by~~



~~— or a pharmaceutically acceptable salt thereof.~~

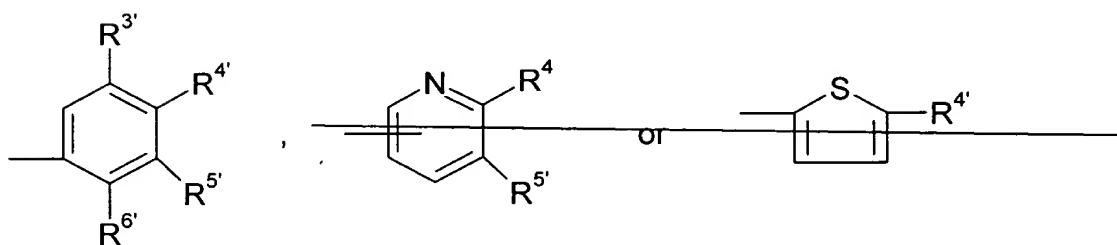
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16. (Amended) A method for the treatment of a cancerous cell growth mediated by raf kinase, according to claim 15, comprising administering a compound of formula IIa:



wherein

A is



R^3 , R^4 , R^5 and R^6 are each independently H, halogen, NO_2 , C_{1-10} -alkyl, optionally substituted by halogen up to perhaloalkyl, or C_{1-10} -alkoxy, optionally substituted by halogen up to perhaloalkoxy, , C_{1-10} -alkanoyl, optionally substituted by halogen up to perhaloalkanoyl, C_{6-12} aryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy, or C_{5-12} hetaryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy,

and either one of ~~R^3 - R^6 can be X-Y~~ R^3 , R^4 , R^5 and R^6 is -M-L¹;

or two adjacent ~~R³-R⁶ can together be~~ of R³, R⁴, R⁵ and R⁶ together are an aryl or hetaryl ring with 5-12 atoms, optionally substituted by C₁₋₁₀-alkyl, halo-substituted C₁₋₁₀-alkyl up to perhaloalkyl, C₁₋₁₀-alkoxy, halo-substituted C₁₋₁₀-alkoxy, up to perhaloalkoxy, C₃₋₁₀-cycloalkyl, C₂₋₁₀-alkenyl,

C₁₋₁₀-alkanoyl; C₆₋₁₂-aryl, C₅₋₁₂-hetaryl, C₆₋₁₂-alkaryl, halogen; -NR¹R¹; -NO₂; -CF₃; -COOR¹; -NHCOR¹; -CN; -CONR¹R¹; -SO₂R²; -SOR²; -SR²; in which R¹ is H or

C₁₋₁₀-alkyl, optionally substituted by halogen, up to perhalo and R² is C₁₋₁₀-alkyl, optionally substituted by halogen, ~~up to perhalo, with SO₂ optionally incorporated in the aryl or hetaryl ring, and R³-R⁶ are as defined in claim 15.~~

R³, R⁴, R⁵ and R⁶ are independently H, halogen, C₁ - C₁₀ alkyl, optionally substituted by halogen up to perhaloalkyl,

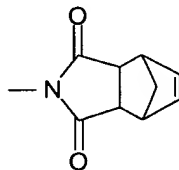
C₁-C₁₀ alkoxy optionally substituted by halogen up to perhaloalkoxy or two adjacent of R³, R⁴, R⁵ and R⁶, together with the base phenyl, form a naphthyl group optionally substituted by halogen up to perhalo, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkanoyl,

C₆₋₁₂ aryl, C₅₋₁₂ hetaryl or C₆₋₁₂ aralkyl, halogen up to perhalo ;

R¹ is C₁₋₁₀ alkyl optionally substituted by halogen up to perhalo;

M is -CH₂-, -S-, -N(CH₃)-, -NHC(O)- -CH₂-S-, -S-CH₂-, -C(O)-, or -O-; and

L¹ is phenyl, pyridyl, naphthyl, pyridone, pyrazine, pyrimidine, benzodioxane, benzopyridine or benzothiazole, each optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen, OH, -SCH₃, NO₂ or, where Y is phenyl, by



or a pharmaceutically acceptable salt thereof.

B

17. A method according to claim 16, wherein

R^3 is halogen or C_{1-10} -alkyl, optionally substituted by halogen, up to perhaloalkyl;

R^4 is H, halogen or NO_2 ;

R^5 is H, halogen or C_{1-10} -alkyl;

R^6 is H [or] C_{1-10} -alkoxy, thiophene, pyrole or methylsubstituted pyrole

$R^{3'}$ is H, halogen, C_{4-10} -alkyl, ~~CH_3~~ , or CF_3 and

$R^{6'}$ is H, halogen, CH_3 , CF_3 or OCH_3 .

18. A method according to claim 16, wherein ~~X~~ M is $-CH_2-$, ~~or~~ $-S-$, $-N(CH_3)-$ or $-NHC(O)-$ and ~~Y~~ L^1 is phenyl or pyridyl.

19. A method according to claim 16, wherein ~~X~~ M is $-O-$ and ~~Y~~ L^1 is phenyl, pyridone, pyrimidine, pyridyl or benzothiazole.